Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, new claims 9-23 are pending in the application, with 9, 11, 21 and 23 being the independent claims. Claims 2 and 6-8 are sought to be cancelled without prejudice to or disclaimer of the subject matter therein. New claims 9-23 are sought to be added. Support for the new claims can be found, for example, in cancelled claims 2 and 6-8 and in the specification at page 10, lines 17-21, page 14, lines 1-11, page 14, line 19-30 - page 15, lines 1-2 and figures 6 and 7. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Obviousness-type Double Patenting

The Examiner has rejected claims 2 and 6-8 under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 2 of U.S. Patent No. 6,183,974 (Paper No. 15, page 2, item 5). Applicants submit herewith a terminal disclaimer to obviate the double patenting rejection over claims 1 and 2 of U.S. Patent No. 6, 183, 974. Accordingly, Applicants respectfully request that the Examiner withdraw the rejection.

Rejections under 35 U.S.C. § 112, second paragraph (indefiniteness)

The Examiner has rejected claims 2 and 6-8 under 35. U.S.C. § 112, second paragraph, for allegedly "failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." (Paper No. 15, page 3, item 6). Specifically, the Examiner states that "[c]laim 2 is vague and indefinite because there is no clear antecedent basis for 'said cells of step (d)'...." Applicants respectfully traverse this rejection.

Solely in an effort to expedite prosecution, however, and without acquiescence in the propriety of the rejection, Applicants have canceled claim 2, from which claims 6-8 depend, and have added new claims 9-23. Thus, the rejection is moot and Applicants respectfully request that it be withdrawn.

Rejections under 35 U.S.C. § 112, second paragraph

The Examiner has rejected claims 2 and 6-8 under 35 U.S.C. § 112, second paragraph for allegedly being incomplete for omitting essential elements, such omission amounting to a gap between the elements...." Applicants respectfully traverse this rejection.

The Examiner states that "[c]learly some comparative step between a cell comprising the recombinant receptor and a cell lacking that receptor would be a minimal requirement for the claimed method to meets its functional requirements." (Paper No. 15, page 4, item 7). Furthermore, the Examiner states that "Applicant can not reply upon what is known in the art to complete the instant claims." Applicants disagree.

Solely in an effort to expedite prosecution, however, and without acquiescence in the propriety of the rejection, Applicants have canceled claim 2, from which claims 6-8 depend, and have added new claims 9-23. Claims 9-11, from which 12-20 depend, now recite "measuring ***and comparing*** the u-PA activity of the cell culture supernatant..." in step (e) of claims 9-10 and step (f) of claim 11. Furthermore, claims 9-11 recite a new step in which it is determined whether a compound of interest affects a Gs and Gq coupled receptor based on the results of the measurement of u-PA activity of the cell culture supernatant. For example, claim 9 recites:

> (f) determining whether a compound of interest affects an adenylyl cyclase or phospholipase C pathway and therefore is an agonist of a receptor which couples to both Gs and Gq proteins, wherein the fluorescence or absorbency spectroscopy values of the cell culture supernatant of said stably transfected cells from step (d) is greater than the fluorescence or absorbency spectroscopy values of the cell culture supernatant of said cells from step (c), which have not been in contact with said compound of interest.

Thus, the rejection is moot and Applicants respectfully request that the rejection is withdrawn.

Rejections under 35 U.S.C. § 101

The Examiner has rejected claims 2 and 6-8, under 35 U.S.C. § 101 alleging that the invention is "inoperative and therefore lacks utility." (Paper No. 15, page 4, item 8). Applicants respectfully traverse this rejection.

The Examiner argues that due to the 35 U.S.C. § 112, second paragraph rejection, the invention is inoperative. However, in light of the above arguments and new claims, this rejection is now moot and should be withdrawn.

Rejections under U.S.C. § 103(a)

The Examiner has maintained the rejection of claims 2 and 6-8 under 35 U.S.C. § 103(a) for allegedly being unpatentable over Catanzariti *et al. BioTechniques* 15:474-479 (1993) ("Catanzariti"), and in view of the combination of the U.S. Patent 5,494,806 to Segre *et al.* ("Segre") and the Bringhurst *et al. Endrocrinology* 132:2090-2098 (1993) publication ("Bringhurst"). Applicants respectfully traverse this rejection.

The Examiner states that "the instant rejection is based upon a premise that the limitation 'a receptor which couples to both Gs and Gq proteins' is inherent to the human parathyroid hormone/parathyroid hormone related peptide receptor (PTHR) of the Segre et al patent...." Paper No. 15, page 5. Applicants respectfully wish to remind the Examiner that inherency and obviousness are distinct concepts and that inherency cannot be made a basis for supporting an obviousness rejection. Furthermore, "A retrospective view of inherency is not a substitute for some teaching or suggestion supporting an obviousness rejection." *In re Rijckaert* 9 F.3d 1531, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993). Applicants respectfully request the Examiner provide such a teaching or suggestion. Applicants raised this issue in the Reply dated October 21, 2002 and requested legal basis for an obviousness rejection based on inherency, which the Examiner has not provided. If inherency is applied to the new claims, Applicants again respectfully request the legal basis

for applying inherency to an obviousness rejection. In the absence of such support the rejection cannot stand.

In addition, the Examiner states that the "...combination of references taught all of the limitations of the instant claims either explicitly or inherently...." (Paper No. 15, page 6). Applicants respectfully disagree as there is no teaching in the cited references for determining whether a compound is an agonist or antagonist of a ***dual*** coupled receptor using the claimed method. Furthermore, Applicants remind the Examiner that "to establish a case of prima facie obviousness of a claimed invention, all the claimed limitations must be ***taught or suggested*** by the prior art." (emphasis added) *In re Ryoka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). MPEP 2143.03. Any suggestion for combining the art cannot come from the Applicants' disclosure. *In re Vaeck*, 20 USPQ 2d 1438, 1442 (Fed. Cir. 1992).

The claims currently being prosecuted relate to a method for determining whether a ***compound of interest*** affects an adenylyl cyclase ***or*** phospholipase C pathway and therefore is an agonist of a receptor which ***couples to both Gs and Gq proteins***. New claims 9-23, that replace claims 2 and 6-8, have been added to more clearly point out this aspect of the invention. The Examiner states that the "instant rejection is maintained because the Bringhurst et al. publication disclosed the production of LLC-PK1 cells which were stably transfected with DNA encoding rat and opossum PTHRs...." However, in Bringhurst, there is no teaching of whether PTHR stimulation by an agonist or antagonist of a Gs and Gq coupled receptor could be detected by an increase in u-PA activity.

Furthermore, there is no teaching of the claimed method in the remaining art cited by the Examiner or a suggestion to combine the additional art with Bringhurst. Catanzariti

is entirely focused on the use of the u-PA response in LLC-PK1 cells to detect responses mediated by receptors coupled ***only*** to Gs. In addition, there is no suggestion in Catanzariti to use the assay described therein to screen for antagonists of Gs coupled receptors. Finally, Segre may mention expressing human PTH/PTHRP receptor in LLC-PK1 cells, however Segre does not suggest that the PTH receptor is coupled to Gs and Gq.

None of the references cited by the Examiner provide a suggestion or motivation to transfect LLC-PK1 cells with a Gs and Gq protein coupled receptor for the purpose of determining whether a compound of interest is an agonist or antagonist of that receptor. Furthermore, none of the references suggest that u-PA can be used as a reporter assay to identify agonists and antagonists of dual coupled receptor. The references could not have suggested the method of the claimed invention as the inventors were the first to identify that receptors, such as PTHR, could activate u-PA by either or both of at least two independent signaling pathways, PKA and PKC.

In any event, solely in an effort to expedite prosecution and without acquiescence in the propriety of the rejections, Applicants have canceled claims 2 and 6-8 and have added new claims 9-23.

Claim 9 claims a method for determining whether a compound of interest is an agonist of a Gs and Gq dual coupled receptor by comparing the u-PA activity of the cell line transfected with the dual coupled receptor to the u-PA activity of the same transfected cells which have not been in contact with said compound of interest. An increase in u-PA activity, relative to the u-PA activity from transfected cells not exposed to said compound, indicates an agonist of said dual receptor.

Claim 10 claims a method for determining whether a compound of interest is an agonist of a Gs and Gq dual coupled receptor by comparing the u-PA activity of the cell line transfected with the dual receptor to the u-PA activity from the starting cell line, which has not been transfected, wherein both sets of cells have been in contact with said compound of interest. An increase in u-PA activity, relative to the u-PA activity from the non-transfected cells, indicates an agonist of said dual receptor.

Claim 11 claims a method for determining whether a compound of interest is an antagonist of a Gs and Gq dual coupled receptor by comparing the u-PA activity of a cell line transfected with the dual receptor wherein the first group of cells is contacted with a known agonist of the dual receptor and the second group of cells is contacted with a known agonist of the dual receptor and then the compound of interest. A decrease in u-PA activity, relative to the u-PA activity from the group of cells contacted only with the agonist, indicates an antagonist of said dual receptor.

New claims 21-23 claim a method for determining whether a compound of interest is an agonist or an antagonist of a receptor which couples to both Gs and Gq proteins thereby affecting an adenylyl cyclase or phospholipase C pathway.

Applicants state that nothing in the references cited by the Examiner teach or suggest the methods claimed in new claims 9-23. In view of the above arguments, and the new claims, Applicants believe that this rejection is now moot and should be withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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Version with markings to show changes made

Claims 2 and 6-8 were canceled without prejudice or disclaimer

New claims 9-23 have been added:

9. (New) A method for determining whether a compound of interest affects an adenylyl cyclase or phospholipase C pathway and therefore is an agonist of a receptor which couples to both Gs and Gq proteins comprising:

(a) providing a cell line which expresses urokinase-type plasminogen activator (u-PA);

(b) providing an expression vector comprising a nucleotide sequence encoding for a receptor which couples to both Gs and Gq proteins, said receptor not normally expressed in said cell line of step (a);

(c) introducing said expression vector into said cell line, thereby providing stably transfected cells;

(d) contacting said stably transfected cells of step (c) with said compound of interest; and

(e) determining whether said compound of interest affects an adenylyl cyclase or phospholipase C pathway and therefore is an agonist of a receptor which couples to both Gs and Gq proteins, wherein the u-PA activity, as measured by the fluorescence or absorbency spectroscopy values of the cell culture supernatant, of said

stably transfected cells from step (d) is greater than the fluorescence or absorbency spectroscopy values of the cell culture supernatant of said cells from step (c).

10. (New) The method of claim 9, wherein the method alternatively comprises:

(d) contacting said stably transfected cells of step (c) and said cell line of step (a) with said compound of interest; and

(e) determining whether said compound of interest affects an adenylyl cyclase or phospholipase C pathway and therefore is an agonist of a receptor which couples to both Gs and Gq proteins, wherein the u-PA activity, as measured by the fluorescence or absorbency spectroscopy values of the cell culture supernatant, of said stably transfected cells from step (d) is greater than the fluorescence or absorbency spectroscopy values of the cell culture supernatant of said cell line of step (d), which is not stably transfected with said receptor.

11. (New) A method for determining whether a compound of interest affects an adenylyl cyclase or phospholipase C pathway and therefore is an antagonist of a receptor which couples to both Gs and Gq proteins comprising:

(a) providing a cell line which expresses urokinase-type plasminogen activator (u-PA);

(b) providing an expression vector comprising a nucleotide sequence encoding for a receptor which couples to both Gs and Gq proteins, said receptor not normally expressed in said cell line of step (a);

(c) introducing said expression vector into said cell line, thereby providing stably transfected cells;

(d) contacting a first group of said stably transfected cells of step (c) with a known agonist of said receptor and then contacting said first group of stably transfected with said compound of interest;

(e) contacting a second group of said stably transfected cells of step (c) with a known agonist of said receptor; and

(f) determining whether said compound of interest affects an adenylyl cyclase or phospholipase C pathway and therefore is an antagonist of a receptor which couples to both Gs and Gq proteins, wherein the u-PA activity, as measured by the fluorescence or absorbency spectroscopy values of the cell culture supernatant, of said stably transfected cells from step (d) is less than the fluorescence or absorbency spectroscopy values of the cell culture supernatant of said stably transfected cells from step (e).

12. (New) The method of claim 9, wherein said Gs and Gq protein coupled receptor is human PTHR.

13. (New) The method of claim 10, wherein said Gs and Gq protein coupled receptor is human PTHR.

14. (New) The method of claim 11, wherein said Gs and Gq protein coupled receptor is human PTHR.

15. (New) The method of claim 9, wherein said cell line is LLC-PK1.

16. (New) The method of claim 10, wherein said cell line is LLC-PK1.

17. (New) The method of claim 11, wherein said cell line is LLC-PK1.

18. (New) The method of claim 15, wherein said Gs and Gq protein coupled receptor is human PTHR.

19. (New) The method of claim 16, wherein said Gs and Gq protein coupled receptor is human PTHR.

20. (New) The method of claim 17, wherein said Gs and Gq protein coupled receptor is human PTHR.

21. (New) A method for determining whether a compound of interest is an agonist of a receptor which couples to both Gs and Gq proteins thereby affecting an adenylyl cyclase or phospholipase C pathway comprising:

(a) providing a cell line which expresses urokinase-type plasminogen activator (u-PA);

(b) providing an expression vector comprising a nucleotide sequence encoding for a receptor which couples to both Gs and Gq proteins, said receptor not normally expressed in said cell line of step (a);

(c) introducing said expression vector into said cell line, thereby providing stably transfected cells;

(d) contacting said stably transfected cells of step (c) with said compound of interest; and

(e) determining whether said compound of interest is an agonist of a receptor which couples to both Gs and Gq proteins thereby affecting an adenylyl cyclase or phospholipase C pathway, wherein the u-PA activity, as measured by the fluorescence or absorbency spectroscopy values of the cell culture supernatant, of said stably transfected cells from step (d) is greater than the fluorescence or absorbency spectroscopy values of the cell culture supernatant of said cells from step (c), which have not been in contact with said compound of interest.

22. (New) The method of claim 21, wherein the method alternatively comprises:

(d) contacting said stably transfected cells of step (c) and said cell line of step (a) with said compound of interest; and

(e) determining whether said compound of interest is an agonist of a receptor which couples to both Gs and Gq proteins thereby affecting an adenylyl cyclase or phospholipase C pathway, wherein the u-PA activity, as measured by the fluorescence or absorbency spectroscopy values of the cell culture supernatant, of said stably transfected cells from step (d) is greater than the fluorescence or absorbency spectroscopy values of the cell culture supernatant of said cell line of step (d), which is not stably transfected with said receptor.

23. (New) A method for determining whether a compound of interest is an antagonist of a receptor which couples to both Gs and Gq proteins thereby affecting an adenylyl cyclase or phospholipase C pathway comprising:

(a) providing a cell line which expresses urokinase-type plasminogen activator (u-PA);

(b) providing an expression vector comprising a nucleotide sequence encoding for a receptor which couples to both Gs and Gq proteins, said receptor not normally expressed in said cell line of step (a);

(c) introducing said expression vector into said cell line, thereby providing stably transfected cells;

(d) contacting a first group of said stably transfected cells of step (c) with a known agonist of said receptor and then contacting said first group of stably transfected with said compound of interest;

(e) contacting a second group of said stably transfected cells of step (c) with a known agonist of said receptor; and

(f) determining whether said compound of interest is an antagonist of a receptor which couples to both Gs and Gq proteins thereby affecting an adenylyl cyclase or phospholipase C pathway, wherein the u-PA activity, as measured by the fluorescence or absorbency spectroscopy values of the cell culture supernatant, of said stably transfected cells from step (d) is less than the fluorescence or absorbency spectroscopy values of the cell culture supernatant of said stably transfected cells from step (e).